

TYPHOID-PARATYPHOID VACCINE IN OCULAR INFLAMMATIONS*

REPORT OF CASES

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WHILE the use of typhoid-paratyphoid inoculations as well as the use of other foreign proteins in the treatment of local inflammatory conditions is not at all a new subject, it was felt that the presentation of the following eye cases treated by the intravenous use of typhoid-paratyphoid vaccine was justified from the standpoint of stimulating local interest in this valuable therapeutic measure.

COMMENTS ON THE LITERATURE

Ichiwaka, Kraus, and Gay treated typhoid patients with typhoid vaccine injected intravenously and observed a sudden drop of temperature and frequent improvement in the general condition of the subject. Miller at Cook County Hospital gave two thousand injections in cases of typhoid and various other conditions with improvement. Peterson also made observations of this sort, and soon various substances were tried, including albumoses, leukocytic extract, gonococcus vaccine, normal serum, etc.

In 1912 Wagner von Jauregg of Vienna noted that patients with general paresis were benefited by attacks of intercurrent disease, and found that tertian malaria was the most promising with its intermittent swing of temperature.

Müller and Thanner then tried milk injections in gonorrheal ophthalmia and observed a distinct benefit from this treatment. It was noted that milk injections were quite specific in acute inflammations of the conjunctiva, but not so decidedly effective where the deeper structures of the eye were involved.

The most outstanding and convincing work in the use of foreign proteins in the treatment of eye diseases, both as to results and methods of use, was accomplished during 1919 to 1927 by Harvey Howard, who was then in charge of the department of ophthalmology at Peking Union Medical College. He made use of dilutions of typhoid-paratyphoid vaccines and injected them intravenously.

TECHNIQUE OF INJECTIONS

The dilutions were made by taking stock typhoid-paratyphoid vaccines and diluting them in the following manner: To one cubic centimeter of vaccine add nine cubic centimeters of normal saline. This may be called solution No. 1. To one cubic centimeter of solution No. 1 add nine cubic centimeters of normal saline. This is solution No. 2, which is a 1-100 dilution of the stock

vaccine. The stock vaccine contains per cubic centimeter:

1,000,000,000 killed typhoid organisms
750,000,000 killed paratyphoid A
750,000,000 killed paratyphoid B

which equals 2,500,000,000 organisms. Hence, one cubic centimeter of solution No. 2 contains 25,000,000 organisms. The initial dose for an individual of 150 pounds in fair general health is 25,000,000 organisms. One cubic centimeter of solution No. 2 is diluted with sufficient normal saline to make five to ten cubic centimeters of solution for injection. The final solutions, as well as the stock solutions, must at all times be clear and free from contaminations. Solutions No. 1 and No. 2 can be kept on ice for a time, seldom over two weeks.

REACTIONS

Systemic.—About one-half hour to one hour after injection the patient develops a chill. During the chill there is a lowering of the systolic blood pressure and a rise in the diastolic. There is also a leukopenia. Within the next two to three hours, the temperature rises to 101 or 103, occasionally to 104 degrees; there is a leukocytosis; the blood pressure returns to normal. The peak is generally reached about four or five hours after injection. Then there is a drop of about an average of one and one-half to two degrees in about two hours, followed by a slow secondary rise and a fall by lysis within twenty-four hours, occasionally lasting forty-eight hours. The leukocytosis and the relative increase of polymorphonuclear cells varies directly as the temperature. The interval between doses depends upon the result obtained; generally a three-day interval is selected, but temperature should be normal before repetition.

Focal.—Howard points out that in the intravenous use of typhoid a focal reaction of the diphasic type such as is observed when milk injections are given intermuscularly is not present, or at least is practically inconspicuous, and this has been our observation in most of the cases.

Results.—Howard presents sixty-two cases of great variety, including acute and chronic inflammations of the uveal tract, various forms of keratitis, corneal ulcers, retrobulbar neuritis, gonorrheal ophthalmia, traumatic cataract, vitreous opacities, with improvement in all but one case of corneal ulcer, one case of chronic iridocyclitis, and in those cases of optic atrophy which he treated.

THEORIES OF ACTION

There are undoubtedly several factors responsible for the improvement:

1. We know there is an increase of the blood antibodies.

2. There is a fever produced, and we know that for the gonococcus the optimum temperature is 36.5 to 37 degrees centigrade for cultures. A sudden rise to 39 degrees centigrade results in death of the culture.

* From the Eye Services of Doctors George H. Kress, George W. McCoy, and William A. Boyce at the Los Angeles County General Hospital, Unit No. 1. Reported with their permission.

* Read before the Eye and Ear Section of the Los Angeles County Medical Society, May 5, 1930.

3. There may be a sudden flooding of the lymph spaces by antibodies after the permeability of the capillaries has been increased following a protein shock.

4. The leukocytosis is probably an important factor.

5. The opsonic index of the blood is raised.

6. There is no direct action on the causative agent as with specific antitoxins, but there is an indirect stimulation producing a pronounced action of the body defense mechanism.

At the Los Angeles General Hospital we have treated twenty-one cases during the past eighteen months by the method outlined above. We do not use it routinely, perhaps not even so often as we might, but have reserved this measure for those cases in which we feel the eye is dangerously involved. Some of the patients had been treated for several weeks by other physicians, who had used the usual local measures without success.

REPORT OF CASES

CASE 1.—A white, male, age seventy-three. Admitted April 30, 1929, complaining of itching, burning, tearing, photophobia and pain in eyeball for six months. He was treated at a local clinic for two weeks, became worse and was then referred to Los Angeles General Hospital, where a diagnosis of acute exacerbation of chronic trachoma with pannus on both corneae and some erosion of epithelium on the right. The tarsal plates were scarred and atrophied. The Wassermann and Kahn tests were four plus. Local treatment for the eyes and general treatment for lues were instituted. For six days no improvement was noted, so it was decided to start him on the non-specific protein therapy. In the first injection 25,000,000 organisms were given intravenously. There was a good general reaction, but the local condition remained stationary. Five days later 40,000,000 bacilli were injected and there was a good reaction systemically, but no local improvement noted until three days later, when they appeared to be much improved. Again they remained quite stationary for about four days and a third injection was given, 80,000,000 organisms. This was followed by rapid improvement, and eleven days later the acute pannus had receded, leaving only the atrophic vascular remains. The patient was discharged seven weeks after entry with condition arrested.

CASE 2.—White, male, age forty-nine, had a cataract extraction by the combined method, left eye, on March 28, 1929, and six weeks later developed an acute phlyctenular keratitis. General examination was negative, tonsils had been removed, sinuses were negative, no focus could be found. Here 25,000,000 organisms were given intravenously and the next day there was marked improvement. He was discharged a week later with condition arrested.

CASE 3.—White, female, age forty. This patient gave a history of having been hit in right eye with an olive pit three weeks previously. Stated that she had no symptoms until two days before coming to clinic, when her vision began to blur. Examination showed an area of deep infiltration in the center of the cornea; the iris was dull and there was marked circumcorneal injection. Local treatment was instituted and the same day 25,000,000 typhoid-paratyphoid organisms were given. There was improvement in the inflammatory reaction the next day, and the case progressed slowly. Five days later 50,000,000 organisms were given. Reaction was rather severe,

and patient suffered considerable headache. Her temperature reached 104. The third injection was, therefore, cut to 75,000,000 instead of doubling the previous dose. The patient was discharged shortly after the third injection with inflammation subsided, and some remaining opacity.

CASE 4.—White, male. Six weeks previous to entry he incurred a corneal abrasion of his right eye from a fall through an orange tree. He was treated by a local eye, ear, nose, and throat physician since the day of his accident, but condition slowly became worse. The right eye contained some thin stringy mucous secretion; there was chemosis of the bulbar conjunctiva. The vessels in the lower quadrant extended to the margins of a deep crescentic corneal ulcer which was about three millimeters at its greatest width and six millimeters long. In the center it had eroded to Descemet's membrane, which glistened through a place about 1.5 millimeter in diameter. The remainder of the cornea was opaque and rough, obscuring details of anterior segment of the eye. Vision was restricted to form perception. Local treatment was instituted; morphin was necessary to control pain. A conjunctival flap was advised, but patient refused, so he was started on a course of typhoid-paratyphoid injections. About 25,000,000 organisms were used for the first injection and the next day the chemosis of the bulbar conjunctiva had receded, and the pain was greatly reduced. Three days later 50,000,000 organisms were given. The ulcerated area was very thin, but not perforated, and the epithelium was beginning to grow over. A third injection was given following which the area completely healed and the depression soon began to fill in. Subsequent local treatment with dionin and yellow oxid of mercury finally resulted in clearing of the cornea to the extent that 20/50 vision had been restored at the last visit.

CASE 5.—White, female, age seventeen. This patient had a shallow ulcer, 1.5 millimeter in diameter, located in the pupillary area of the right eye. She was treated with the thermophore at 150 degrees Fahrenheit for one minute and the ulcer healed. She returned five months later with an area of deep infiltration in center of cornea which had broken down and ulcerated. It was thought too deep for the thermophore, so typhoid vaccine, 25,000,000 organisms, was given and the accompanying inflammatory signs began to clear. Three days later 40,000,000 organisms were given. The ulcer was curetted to Descemet's membrane, a pressure bandage applied, and the lesion healed.

CASE 6.—White, male, age sixty-nine. The patient stated that he was struck in the right eye with a tree limb three weeks previous to entry. He had been treated during this time by another physician, without relief. Examination revealed a dilated pupil with incarceration of the iris, and dislocation of the lens downward into the vitreous beyond the ciliary body. The eye was sensitive to light and very painful. The tension was minus two; general examination was negative. He was given 25,000,000 organisms and the next day his photophobia and pain was decreased. He was discharged with a quiet eye, but the vitreous was full of opacities of the heavy stringy variety.

CASE 7.—White, male, age twenty-three. Presented himself for examination, complaining of photophobia, lacrimation, and a feeling of tenseness in the eye for two days. The pupil was small and spastic; the iris was dull; the circumcorneal vessels were injected. The vitreous showed some faint opacities. A diagnosis of acute uveitis was made, local treatment instituted, and 25,000,000 organisms were given. The

temperature reached 104.4 degrees and the patient complained of headache, insomnia, and backache so pronounced that morphin was given to put him at rest. The next day the eye was greatly improved and in seven days local treatment was discontinued. An infected tonsil tag, the only focus found was subsequently removed. There has been no recurrence in one year.

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CASE 8.—White, male, age twenty-three. Admitted with an acute follicular conjunctivitis. Smears were negative for bacteria. He had been treated for one month without improvement. The first injection of typhoid organisms resulted in improvement and two more completed resolution of the process without local treatment other than atropin and soothing ointments.

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CASE 9.—White, male, age nineteen. This patient suffered a severe ulcerative keratitis involving both corneae: one lesion on right cornea, four millimeters in diameter; three ulcers on left cornea, two to three millimeters in diameter. Dense infiltration and panus surrounded the lesions. General examination negative except for chronic tonsillitis. Treated locally, tonsils were removed and there was marked improvement, but resolution was slow, so two injections of typhoid vaccine were given and in five days healing was complete. He was discharged with a visual acuity: 20/40, right eye; 20/100, left eye.

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CASE 10.—White, male, age forty-one. This patient had a case of old trachoma with corneal ulcer in left eye. He was given four injections of typhoid vaccine intravenously, and the ulcer healed.

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CASE 11.—White, female, age thirty-eight. This patient was operated for an old, tough capsular cataract, the result of a penetrating injury with a needle during childhood. The operation was followed by a low-grade iritis, which was treated with atropin locally and salicylates internally. Progress was slow, so patient was given 25,000,000 organisms and after a good systemic reaction the eye quieted in a few days.

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CASE 12.—White, male, age twenty-eight. He was admitted to the hospital with an old trachoma; tarsal cartilages had been removed. On admission he had a subacute pansinusitis with flare-up of the eyes. He was undernourished; Wassermann was negative; dental examination was negative. He was started on a series of injections with immediate improvement after first injection and arrest of eye condition after third injection. Treatment of the pansinusitis was under way after second injection and continued for some time after. He returned to the eye clinic in five months with another acute exacerbation of eye condition, recurrence of panus, and a corneal ulcer. Another course of intravenous injections of the vaccine was given, a series of five being required before the condition was arrested. The ulcer was healed after the second injection. The eyes have been quiet for six months.

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CASE 13.—White, female, age fifty-four. A debilitated little old woman, trephined two years previously, came in with a late infection of the operated eye, consisting of an iridocyclitis with secondary elevation of the intra-ocular tension. A series of intravenous injections was started. Two treatments showed that this method was impracticable. She was emaciated and the fever produced burned up what reserve she had, resulting in increased general weak-

ness and no response from the debilitated tissues to stimulation. Hence there was no improvement whatever in her eye condition after two injections and the treatments were discontinued because of this and her general condition. An attempt was made to improve her nutrition, with some success, and a second series was tried, starting with 12,000,000 organisms, but two injections sufficed to show that she could not stand further fever reactions. A trephine was done below and the facilitated lymph flow improved the condition temporarily, but in four weeks exudation increased and filled the pupillary area.

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CASE 14.—White, male, age thirty-eight. This patient was admitted with inflammation of the left eye, consisting of marginal blepharitis, chronic conjunctivitis, and a marginal crescent-shaped ulcer on the temporal side, measuring six millimeters in length and three millimeters at its greatest width. General examination was negative except for chronic tonsillitis. He was given the usual dose of typhoid vaccine the day of his admission, and improvement was noted the next day. In five days the ulcer had healed without further vaccine therapy. His tonsils were then removed. In two months he returned with a recurrence, and after two injections the ulcer was healed with no recurrence in the past three months.

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CASE 15.—White, male, age twenty-seven. A large central ulcer, six millimeters in diameter with a circle of infiltration which stained by absorption, occupied the center of this man's cornea. Local medication was started and a day later the typhoid vaccine was given; three days later a second injection, and in three days more the ulcer was healed. There has been no recurrence in one year's time.

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CASE 16.—White, male, age sixty-two, in excellent health. Several weeks following a cataract operation a low-grade uveitis developed, the vitreous slowly filled with small opacities and finally a secondary glaucoma developed. All possible foci of infection had been taken care of previous to operation and no further evidence could be found. A series of typhoid injections were given, without improvement.

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CASE 17.—White, male, age forty-five. In this man an old trachoma flared up, complicated by a small corneal ulcer. One injection sufficed to heal the ulcer, and local treatment was continued for the trachoma. In eight months he had a recurrence with a large, deep ulcer, about three millimeters in diameter, with anterior synechia. Two injections of typhoid were given and the ulcer healed, with an adherent leukoma as the end result.

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CASE 18.—Colored, female, age nineteen. This patient came to the hospital with both corneae involved. The right was deeply infiltrated and there were several small ulcers on the surface. The left cornea was infiltrated, but none of the areas had broken down to ulceration. She was hospitalized and given 25,000,000 organisms. Her temperature reached 103. The next two days showed a very striking improvement in her condition. After two injections the ulcers had healed and the inflammation almost entirely subsided. A third treatment was given and the patient was discharged with the condition arrested.

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CASE 19.—White, male, age sixty-two. In this man striate keratitis persisted for fifteen days after cataract extraction and did not show signs of improving,

so 15,000,000 typhoid organisms were given intravenously and in two days the cornea cleared. His visual acuity or refraction was 20/30.

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CASE 20.—White, male. This patient suffered a persistent marginal blepharitis complicated by a secondary pyogenic infection, and superficial keratitis in left eye. He was treated locally for two weeks and finally 25,000,000 of typhoid organisms were given and the inflammation subsided in three days.

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CASE 21.—Colored adult female. To approximate a lacerating wound of the upper lid, linen stitches had been used on skin and conjunctival surfaces, and abrasion of the cornea followed by infection and ulceration with hypopyon resulted. She was given 25,000,000 organisms; the cornea healed and the hypopyon absorbed within a few days.

INDICATIONS (FOUND EFFICACIOUS, ACCORDING TO HOWARD)

1. Acute or subacute infections of the conjunctiva when the disease was unusually severe or prolonged.
2. Ulcers of the cornea and all forms of keratitis.
3. Uveitis, iridocyclitis, and iritis, no matter what cause, with the exception of tuberculosis.
4. Optic neuritis, especially the retrobulbar type and those apparently due to focal infection.
5. Edema of the retina, retinal hemorrhages; and exudative chorioretinitis.
6. Hemorrhages and exudates from the retina or choroid into the vitreous; also acutely developing vitreous opacities, particularly those of the massive dust-like type.
7. The absorption of soft lens material following traumatic cataract or discission of a congenital cataract, or following a cataract extraction in which considerable lens substance was left behind.
8. Penetrating wounds of the eye in order to prevent endophthalmitis or panophthalmitis (an exceedingly important use).
9. Secondary glaucoma, to reduce intra-ocular tension, especially when associated with an inflamed iris and a turbid aqueous.

CONTRAINDICATIONS (Howard)

1. The presence of more than one-half degree centigrade of temperature above normal.
2. Low vitality.
3. Any condition in which the added strain occasioned by a protein shock might not be well borne by the heart.

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COMMENT

It is to be emphasized that the method is not curative and does not relieve us of the obligation of eliminating foci of infection, nor are we justified in neglecting such local treatment as the case may require, such as atropin, antiseptics, ointments, etc. Subsequent local treatment may be required.

MEDICAL MILITARY PREPAREDNESS*

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ONE year ago a brief report was made and some instances of medical military unfitness that this Government experienced in the World War were cited.

Today, following considerable correspondence with such men as the editors of the *Military Surgeon*, of *Foreign Service*, of the *American Veteran*, of *American Legion*, and of the *Journal of the American Medical Association*, and with Colonel Taylor, editor of the *Texas State Medical Journal*, and with the Surgeon-General of the United States Army, I think I have a few more practical ideas to place before you on the important matter of medical military preparedness.

Prior to America's entrance into the World War, sensing the coming storm, a General Medical Board was created and competent men appointed whose duty it was to make a general survey of medical men, hospitals, and medical equipment. Also some fifty medical societies were called upon to suggest specialists for work along their lines.

While this committee did everything in its power to make medical preparation for war, the time was too limited to work the medical personnel of a nation into an organization that could promise much results. The creation of a Medical Officers Reserve Corps in 1910, of which I became a member in 1911, created one rank only, that of first lieutenant. But there was no effort made to train these Reserve Corps officers, and matters simply slid along without care or concern to the average physician until he was rudely awakened by the entrance of the United States into the World War.

We went into this World War practically without trained men or military or naval equipment. It is true we had a small army and navy and a National Guard, but we had neither submarines nor aircraft, and were destitute of the material needed to equip a considerable army and navy; and to create an air force we had neither trained men nor material. When one considers that in the brief time which the war lasted it is one of the modern miracles and a tribute to our Government that such gigantic tasks of organization, training, and equipment were accomplished in so short a time.

To muster and equip an army of over four million men, to build up a naval personnel, to build up an aircraft force, to transport over two million men 2700 miles over seas through enemy zones, to provide food, shelter, clothing, and equipment in so short a time is, without exaggeration, one of the great events of our history. As I said a year ago, we, like the British, muddled through it somehow. Our initiative and inexhaustible resources made us winners, but at fearful financial cost of nearly forty billions of dollars

* Read before the Nevada State Medical Society at Ely, Nevada, September 18 and 19, 1931.